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The variant race is upon us

Several countries are at a point in their vaccination drives where immunity-escaping covid-19 variants are most likely to emerge, reports **Michael Le Page**



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People meet in central London as restrictions lift in England on 19 July

Higher infectiousness is the most worrying trait that the virus can evolve, because it makes it much harder to control. A more transmissible virus will kill more people even if it is no more virulent, because it will infect more individuals.

Higher transmissibility also means a higher proportion of a population needs to be immune to achieve the herd immunity threshold, which is perhaps now as high as 90 per cent compared with around 70 per cent for the original virus.

What's more, infectiousness is often linked to immune evasion. If a virus replicates faster, says Gupta, it takes more antibodies to mop up all the viruses, which means an immune response that works against earlier variants could be overwhelmed.

The good news is there is a limit to how much more transmissible the virus can become. "I think at some point transmissibility will plateau – the virus won't keep getting more transmissible forever," says Jesse Bloom at the University of Washington in Seattle.

However, that might take many more years or even decades. "I'd be cautious about saying that we are nearing its limit. We don't know where that is," says Gupta. "At the moment, the virus is basically saying there is no end to this."

Some have suggested that there is also a limit to how much the coronavirus can evolve to evade immunity. The most effective antibodies bind to the parts of the outer spike protein of the virus that help it infect cells, so it is thought that these parts cannot change much if the

BACK in March, an eventual end to the coronavirus pandemic appeared to be in sight. The number of covid-19 cases were plummeting in the UK and the US as vaccination levels rose. It seemed the same might gradually happen in country after country around the world.

But then India was hit by a devastating second wave, due largely to a new variant now known as delta. After delta spread to many other countries, case numbers soared once again, including in the UK and US.

The question is, will this keep happening? Will more dangerous variants keep evolving, causing fresh waves of infections around the world despite vaccine roll-outs? The answer is almost certainly yes. "Variants will

continue to arise, there's no doubt," says Ravi Gupta at the University of Cambridge.

The SARS-CoV-2 coronavirus mutates relatively slowly compared with some similar viruses. Because of this, there were hopes early in the pandemic that the virus wouldn't change much and that the pandemic would come to a swift end as people acquired immunity through infection or vaccination.

It is now clear that those hopes are forlorn. SARS-CoV-2 has been evolving right from the start. Most mutations either make no difference to the virus's behaviour or are harmful to the virus and so the viruses carrying them die out. But in March 2020, a mutation called D614G appeared that is now thought to make the

virus 50 per cent more infectious. Although it was never given a specific name, it rapidly became the predominant variant.

In September, a variant with 23 mutations compared with the original virus was detected in the UK. Alpha, as it is now known,

"Transmissibility will plateau – the virus won't keep getting more transmissible forever"

is around 50 per cent more transmissible than D614G and it also spread around the world. Now, we have delta, which is about 50 per cent more transmissible again – and can also evade immunity to some extent, like the beta and gamma variants, two other "variants of concern".



virus is to remain able to do this.

The bad news is that new work by Bloom suggests that this belief is wrong and there is no limit to how far the virus can mutate to escape antibodies. "I expect [this kind of] change to continue forever," he says.

Until this work, it wasn't clear whether the pre-existing human coronaviruses that are one of the causes of the common cold persist in people because our immunity to them is short-lived or because they keep evolving to evade our immunity. By analysing blood samples from as long ago as the 1980s, Bloom's team has now shown that their persistence is due to the continual emergence of so-called escape variants.

If SARS-CoV-2 evolves like these other human coronaviruses, it will continue to acquire mutations that enable it to escape the recognition of antibodies, says Bloom. "I don't expect any real end to this process." Other viruses, such as flu, never run out of ways to dodge our immunity, he says.

Evolutionary pressure

Not only may there be no limit, there is also growing evolutionary pressure favouring the emergence of further escape variants. For a virus to evolve, two key things need to happen: the virus has to mutate inside a body and that mutant virus has to spread to other bodies.

If a person with no immunity to the coronavirus breathes in a lot of the virus, it can readily replicate in the upper airway. A virus with a mutation that boosts infectiousness, such as D614G, can have an advantage. It will replicate faster than the original virus and so will have a better chance of being passed on to other people.

However, mutations that help

the virus dodge antibodies won't provide any advantage because that person doesn't yet have antibodies to the coronavirus. There is only a brief window when antibody production kicks in where antibody evasion provides any advantage.

In many countries, however, lots of people now have some immunity due to vaccination or

previous infection. In individuals with high antibody levels, any viruses breathed in will be quickly mopped up. There is almost no chance for mutations to occur, let alone spread to another person.

Unfortunately, a lot of people have only partial immunity. This may be because they have had only one dose of a vaccine, they received one of the less effective

vaccines, they didn't respond that strongly after being infected or vaccinated, or their prior immunity has started to wane.

In these people, antibodies – albeit a limited number – are present right from the start of an infection. Any virus that mutates in a way that helps it dodge those antibodies will have a big advantage and may rapidly come to outnumber the original variant, giving it a much higher chance of being passed on.

When the level of immunity in a population is low, there is little selective pressure for escape variants to emerge, says Aris Katzourakis at the University of Oxford. When this level is very

"I don't expect any real end to the process by which the coronavirus will continue to acquire mutations"

high, it becomes very hard for the virus to spread. "Even if an escape variant emerges, it would fizzle out," he says.

In between these two extremes is a point where escape variants are most likely to evolve and spread. The UK is probably now at this point, says Katzourakis, with reasonably high vaccination levels, but also lots of cases.

There are many other countries with large numbers of cases and high levels of partial immunity due to vaccination or past infection, however, so the UK is far from the only place where new escape variants are likely. It could happen anywhere where the virus is spreading – and in several ways.

For instance, the virus can linger for months in people with weak immune responses, potentially acquiring multiple mutations. Alpha might have evolved this way. In the US alone, there are 10 million people whose

Is an exit wave a real thing?

The current wave of cases in the UK as restrictions are relaxed is being described as an exit wave. This term implies it will be the last wave the country will see, but many experts think there will be more.

"The idea that that's the end of it – unfortunately not," says Aris Katzourakis at the University of Oxford. "We may be undergoing this harm for no long-term pay-off."

In fact, there could be more waves even without new variants emerging. "If there's waning immunity or if contact rates go up, then we will see future waves as well," says Graham

Medley at the London School of Hygiene & Tropical Medicine.

"It is a bit of a euphemism to call it an exit wave."

It has also been suggested that a big exit wave is inevitable whenever restrictions are relaxed, but Katzourakis disagrees. "If you vaccinate enough people before exiting, the size of the wave will always be smaller, perhaps so small as to be imperceptible," he says.

The optimistic scenario is that as countries roll out vaccines and ease restrictions, SARS-CoV-2 will start to behave like a cold virus, circulating at a low level and causing only mild cases, like the existing human coronaviruses.

Unfortunately, getting to this point could take years or even decades, says Katzourakis – if it happens at all. SARS-CoV-2 could instead behave more like flu, with new variants causing occasional waves and pandemics with a substantial death toll.

There is also a grim reason why some common viruses do little harm. "The virus could become benign by killing off all of the people in the population that are susceptible to it," says Katzourakis. "That, to put it mildly, is not something we'd want to let happen."

A covid-19 patient is treated in Queen Alexandra Hospital in Portsmouth, UK



ADRIAN DENNIS/JAP VIA GETTY IMAGES

immune systems are compromised.

The virus could also jump to animals, acquire new mutations and then jump back into people. This has happened at least once, with mink in Denmark, but fortunately the resulting variant wasn't especially dangerous.

And if a person gets infected by more than one variant at a time – or by a SARS-CoV-2 variant and one of the human coronaviruses that causes the common cold – the genomes of the viruses could merge through a process called recombination to create a hybrid.

There is no way to predict when or where this will occur, or how bad the result will be. But what is generally agreed is that the fewer cases there are, the lower the risk of these things happening, says Katzourakis.

This means the best strategy for avoiding the evolution of escape variants is to keep cases as low as we are able while vaccinating populations as fast as possible, he says – to cross the point of maximum risk as quickly as we can, rather than lingering there.

"If enough people are vaccinated and have strong immune responses, we get there quickly without having escape [variants occurring] in the interim," says Katzourakis.

This obviously cannot be achieved by natural infection, by letting the virus rip through a population with no restrictions.

Deadlier variants?

What's more, Bloom and his colleagues have shown that vaccines tend to elicit a wider range of the most effective antibodies, the ones that bind to those key parts of the spike protein, than infection does. In other words, it might be harder for the virus to

"The best strategy for avoiding 'escape variants' is to keep cases low while vaccinating fast"

13.8%

of the world's population is fully vaccinated as of 26 July

A vaccination site in Florida, a state in which cases are surging

escape vaccine-induced immunity than natural immunity.

In addition to evading immunity, new variants could also become more deadly. While it is often said that viruses evolve to cause milder disease, this is no longer thought to be the case. On the contrary, there are several reasons to think SARS-CoV-2 could become more lethal.

For starters, people with covid-19 are most infectious just before symptoms appear, so causing more severe disease has little effect on the virus's chance of spreading.

Some studies suggest that variants such as delta are also evolving the ability to spread directly from cell to cell, rather than via the blood, enabling them to dodge antibodies. This process can cause cells to fuse together, seriously damaging tissues.

"This would be consistent with increased cell-to-cell spread leading to higher virulence," says Shan-Lu Liu at the Ohio State University. However, his team has only demonstrated this type of spread in the lab, not in infected individuals, he cautions.

Another reason why some viruses evolve to cause milder infections is because they become optimised to target our upper airways, as pointed out by Amalio Telenti at Scripps Research and his colleagues in a recent paper in *Nature*. In the upper airway, viruses shed by cells are much more likely to be breathed out and infect others, when compared with viruses that zero in on our lungs. But the receptor targeted by SARS-CoV-2 is also present lower down in the respiratory system, so this doesn't apply.

On the plus side, a growing number of studies show that several vaccines still provide excellent protection against severe disease and death even if they are slightly less effective at preventing infection by new variants such as delta. The expectation is that this protection will only be lost slowly. "The erosion of antibody recognition is gradual," says Bloom. "It will likely take many mutations accumulated over multiple years."

If that is the case, in high-income countries at least, there will be plenty of time to roll out booster shots before any variants completely escape any vaccine. Some vaccine companies have already developed booster shots that should be more effective against new variants.

It might also be possible to develop vaccines that provide protection against a much broader range of variants.

Despite vaccines being our best bet against new variants, so far only about 13.8 per cent of the world's population is fully vaccinated.

Many countries now face their greatest threat during the pandemic, says Katzourakis. "With the delta variant [spreading] in some parts of the world, things are about to get a lot worse." ■



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